reorientation in the crystal lattice than in solution. The fact that the water comes out of the crystal so easily when hydrated TNS crystals are left to dry can be taken as evidence that solvent reorientation can indeed occur in the crystal lattice.

Förster[20] has suggested that fluorescence of the anilinonaphthalenesulfonates is observed only when the two rings are planar. Although steric interactions would not allow complete coplanarity, it may be that the resonance delocalization of electrons over the whole molecule suggested for TNS, a property dependent on degree of planarity of the molecule, may be a factor in determining fluorescence behavior. If upon ultraviolet absorption this electronic delocalization stability is lessened, solvents with strong hydrogen bonding properties and appropriate steric size may lower the energy of the excited state by H···N(16) interaction. Also, the geometry of protein binding sites to which TNS is attracted, not only the polarity of such sites, may affect the energy difference between ground and excited states of the probe molecule and influence its emission characteristics. For example, TNS binds to both chymotrypsin and chymotrypsinogen with dissociation constants that differ only by a factor of 2, yet the probe's fluorescence intensity is many times stronger when bound to chymotrypsin than when bound to the zymogen.[21] It is therefore not entirely safe to assume that such probes measure only the polarity of the binding site, as has been suggested.[22] On the other hand, compounds without the extended resonance possible in TNS, for example, 1-dimethylaminonaphthalene-6-sulfonamide,[23] could be used as probes of polarity without fear of the additional complication of altering the structure of the probe.

An elucidation of the arrangement of water molecules about TNS in the hydrated crystals may be extremely significant in more specifically relating structure to fluorescence properties.

Molecular Packing. Short contacts between molecules occur between H(14) of molecules related through a center of symmetry and between O(3) and O(5) and K^+ of neighboring molecules. The H···H distance is 2.1 Å (van der Waals contact is 2.4 Å) and O(3)···K^+ (x, $1 + y$, z) and O(5)···K^+ ($1 - x$, $1 - y$, $2 - z$) distances are 2.68 and 2.60 Å, respectively (van der Waals contact is 2.73 Å).

Acknowledgments. We thank Professor Martin Gouterman for aid in measuring the crystal fluorescence spectra, Professor Philip Wilcox for supplying the TNS and for helpful discussions, and the National Institutes of Health for support through Grant No. GM-13366.

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Kinetics and Mechanism of the Morpholine–Borane Reduction of Methyl Alkyl Ketones

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Abstract: Deuterium labeling shows that hydrogen is transferred from boron to the carbonyl carbon atom in the reduction of acetone by morpholine–borane *via* both acid-independent (second-order) and acid-catalyzed (third-order) paths. The second-order reaction exhibits a negligible solvent isotope effect and a small (10%) normal B–H substrate isotope effect and is presumed to involve the rate-determining attack of amine–borane on the neutral ketone. The acid-catalyzed reaction exhibits a small substrate isotope effect (20%), but shows a pronounced inverse solvent isotope effect [$k_2(D_2O)/k_2(H_2O) = 2.8$] which suggests a rate-determining attack of amine–borane on a protonated carbonyl which is formed in a rapid preequilibrium. From data on ketone basicity, it is calculated that protonation renders the carbonyl compound about 10^{11} times more reactive toward reduction by morpholine–borane. For the acid-independent path, a transition state requiring some specific orientation of reactants is proposed consistent with activation parameters of 11.0 kcal/mol and −40 eu. An analogy to certain cycloaddition reactions is suggested. Correlation of rates with Taft σ^* parameters for C-alkyl substituents in the ketone suggests that boron–oxygen bond formation may be important in this transition state. It is speculated that the protonated carbonyl may serve as a general acid promoting decomposition of the amine–borane in a manner analogous to the proposed mechanism for acid-catalyzed amine–borane hydrolysis.

In recent years, the rates of amine–borane reductions of various aldehydes and ketones in aqueous solution have been shown to be enhanced by an increase in acidity, and specific kinetic studies have led to rate expressions which indicate reduction to occur by two pathways, one independent of, and the other first order in, hydrogen ion (eq 1).[2] Also characteristic

$$\frac{-\mathrm{d[amine\text{–}borane]}}{\mathrm{d}t} = \mathrm{[amine\text{–}borane][RCOR'][}k_1 + k_2(H_3O^+)] \quad (1)$$

of such systems is the fact that, in addition to the

(1) TCU Research Fellow, 1965–1967. NASA Trainee Fellow, 1967–1969. Presented in part at the Southwest Regional Meeting of the American Chemical Society, Little Rock, Ark., Dec 7–9, 1967.

(2) H. C. Kelly, M. B. Giusto, and F. R. Marchelli, *J. Amer. Chem. Soc.*, 86, 3882 (1964).

Table I. Product Distribution in the Morpholine–Borane Reduction of Acetone at pH 3.1 and 25°

$[CH_3COCH_3]_0$,[a] M	CH_3COCH_3 Initial[b]	CH_3COCH_3 Final[b]	$O(CH_2)_4NHBH_3$ reacted[b,c]	H_2 produced[b]	$(CH_3)_2CHOH$ produced[b]	$(CH_3)_2CHOH$ produced/$O(CH_2)_4NHBH_3$ reacted (mol ratio)
0.13	6.6	5.6	0.83	1.6	0.81	0.98
0.22	5.5	4.3	0.78	1.5	0.79	1.0
1.1	27.3	21.1	0.81	1.3	0.94	1.2
3.0	27.3	25.6	1.3	2.0	1.9	1.5
10.9	27.3	23.1	1.1	1.3	2.0	1.9

[a] Initial concentration of acetone. [b] Mol × 10^3. [c] Represents consumption of >99% of the morpholine–borane introduced into reaction mixture.

formation of the corresponding alcohol as a reduction product, hydrogen is evolved even under conditions in which hydrolysis of the amine–borane itself is negligible. An example of this behavior is found in the morpholine–borane reduction of acetone, and since the relatively high hydrolytic stability of morpholine–borane enables its study as a reducing agent over a wide range of hydrogen ion concentration (pH >3), this system was chosen for a more detailed study of this type of hydride reduction.

In a recent paper, the product (2-propanol and hydrogen) distribution for the morpholine–borane reduction of acetone at pH 5, where only the acid-independent reaction is significant, was reported.[3] Subsequent investigations, including those of substrate and solvent isotope effects, the influence of C-alkyl substitution in the carbonyl compound, and effects of temperature on rate now have been made in an effort to further define details of the mechanism of both the acid-catalyzed and uncatalyzed paths.

Experimental Section

Materials. Carbonyl compounds obtained (Matheson Coleman and Bell) include spectroquality acetone, which was used without further purification; methyl ethyl ketone, which was purified by distillation, bp 79°; and *p*-methoxybenzaldehyde, which was purified by distillation at reduced pressure, bp 97.5° (7 mm). Methyl *t*-butyl ketone, obtained from K and K Laboratories, also was distilled prior to use, bp 106°. The *p*-hydroxyacetophenone (Eastman) was recrystallized three times from benzene, mp 108°. Morpholine–borane was obtained as previously described, and morpholine–borane-d_3 prepared by a procedure previously used for the preparation of *p*-toluidine–borane-d_3.[4] A comparison of intensities of absorption bands in the B–H and B–D stretching regions of the infrared (2325 and 1775 cm^{-1}, respectively) indicated the isotopic purity of morpholine–borane-d_3 to be ≥98%. Dioxane, obtained from Eastman, was boiled under reflux with potassium hydroxide pellets for 1 day, decanted onto lithium tetrahydroaluminate (Ventron Corp.), and, after several hours of boiling under reflux with this reagent, collected by fractional distillation, bp 101°. Deuterium oxide of 99.7% isotopic purity was obtained from New England Nuclear Corp. Potassium acid phthalate-d_1 was obtained by dissolving potassium acid phthalate in D_2O, allowing the solution to stand in a stoppered flask for several days at room temperature, and removing the solvent by evaporation *in vacuo*.

Product Distribution. The apparatus and procedure was similar to that described for the determination of product distribution in neutral aqueous acetone.[3] A chloroacetic acid–chloroacetate buffer was used to maintain the solutions at about pH 3.1. Since the hydrolysis of morpholine–borane is subject to acid catalysis,[4] a separate experiment was carried out in which a solution containing 0.032 *M* morpholine–borane and 1 *M* chloroacetic acid at pH 3.1 was allowed to stand 24 hr at 25°. Subsequent iodate analysis showed loss of less than 7.6% of the original hydride. Since the duration of a product distribution study in aqueous acetone at pH 3.1 was about 2.5 hr, losses of hydride and evolution of hydrogen *via* direct hydrolysis of amine–borane during this period were negligible.

Kinetic Studies. A Freas water bath (Precision Scientific Co.) was used to maintain temperatures (within ±0.02°) of 10, 25, 30, and 40°. For a given rate study, a solution of aqueous acetone was added to a weighed sample of morpholine–borane which had been equilibrated at the same temperature. The initial time, t_0, was taken as the time of addition. The quantity of soluble hydride present at various times was determined iodometrically.[5] For studies in which the acid-dependent path makes a significant contribution to the overall rate of reduction of ketone (pH <5), solutions were buffered using potassium acid phthalate. In all experiments, a large excess of ketone was used, resulting in a "pseudo"-first-order (in amine–borane) kinetic relationship. Ketone concentrations ranged from 0.04 to 0.81 *M*, while initial concentrations of morpholine–borane ranged from 0.0025 to 0.01 *M*. In one series of studies, a *p*-methoxybenzaldehyde concentration of 0.02 *M* and initial amine–borane concentration of 5×10^{-4} *M* were employed. Observed rate constants were obtained from the slopes of the appropriate plots of log [amine–borane] *vs.* time. The rate constant for the acid-independent path, k_1, is equal to the observed rate constant for the reaction in neutral solution. The rate constant for the acid-dependent path was obtained from the slope of the corresponding plot of k_{obsd} *vs.* $[H^+]$, which was constructed from a least-squares treatment of the data. Substrate isotope effects were obtained by separate measurement of the rates of reaction of acetone with morpholine–borane and morpholine–borane-d_3. Solvent isotope effects were obtained by measurement of rates in deuterium oxide at given deuterium ion concentrations.

Determination of Deuterium Ion Concentration in Deuterium Oxide. Acidic deuterium oxide solutions were prepared by adding silicon tetrachloride and potassium acid phthalate-d_1 to deuterium oxide and removing insoluble material by filtration. The desired values of pD were approximated by adjusting the acidity of the solution while obtaining readings on a Beckman Expandomatic pH meter and using the relation[6] pD = pH + 0.4. A final determination of the pD of each solution was calculated following a spectrophotometric determination of the fraction of an appropriate indicator (either bromphenol blue or 4-chloro-2,6-dinitrophenol) in its basic form in the respective solution, and from a knowledge of the dissociation constant of the indicator in deuterium oxide.[7] Absorbances were measured with a Cary 15 recording spectrophotometer.

Product Labeling. About 0.18 g of morpholine–borane-d_3 was added to 10 ml of a 5.5 *M* solution of acetone at pH 5. This solution was allowed to stand for 2 days at 25°, following which the product alcohol was collected by fractional distillation, bp 75°. A similar experiment was performed with 0.20 g of morpholine–borane-d_3 and 5.5 *M* acetone at pH 3. Proton nuclear magnetic resonance spectra of the products were obtained using a Varian A-60A spectrometer.

Studies of Substrate–Solvent Hydrogen Exchange. In a typical experiment, 20 ml of an aqueous solution buffered at pH 2.7 was added to 0.08 g of morpholine–borane-d_3 and the solution maintained at 25° for 35 min. A 3-ml portion of the resulting solution was neutralized with sodium hydroxide solution, the water removed *in vacuo*, and the infrared spectrum of the solid product obtained on a KBr wafer using a Perkin-Elmer Model 137 infrared spectropho-

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tometer. Similar experiments were performed using morpholine–borane and deuterium oxide solutions of pD 2.7 and 4.0.

Results

Product Distribution and Labeling. Product distribution for the reaction of morpholine–borane with acetone at pH 3.1 representing a composite influence of both acid-independent and -dependent paths is shown in Table I. All hydridic hydrogen originally present in the borane is used for the reduction of ketone or evolved as hydrogen gas, as shown by the fact that the total molar quantity of 2-propanol and hydrogen produced equals three times the molar quantity of amine–borane consumed (the fraction of hydridic hydrogen used to reduce the ketone is the mole fraction of 2-propanol in this product mixture). Product distribution for this reaction at pH 5, where reduction of ketone occurs only *via* the acid-independent pathway, has been previously reported.[3] The results at pH 3.1 are similar to those obtained at higher pH in that, even in very dilute acetone, at least one hydridic hydrogen atom per $-BH_3$ unit is used for reduction of the ketone, but differ in the extent to which reduction occurs in concentrated solution. Thus, in 11 *M* acetone, reaction *via* the acid-independent pathway alone leads to utilization of 90% of the available hydride for ketone reduction, as opposed to somewhat less than two-thirds of the available hydride at pH 3.1.

Exposure of morpholine–borane to acidified deuterium oxide (pD 4 or 2.7) at 25° showed no evidence of exchange of hydrogen between hydride and solvent in a period of time during which, in the presence of quantity of ketone used for a typical run (0 81 *M*), consumption of over 95% of the available hydride would have occurred. Similarly, the exposure of morpholine–borane-d_3 to a buffered aqueous solution (pH 2.7) at 25° for a comparable period of time resulted in only a small amount of exchange as evidenced by a comparison of intensities of infrared absorption bands in the recovered deuteride in the BH (2300–2400 cm^{-1}) and BD (1700–1800 cm^{-1}) stretching regions (estimated $I_{BH}/I_{BD} < 0.1$). Thus, hydride exchange is very slow relative to the rate at which the reduction of the acetone occurs, indicating that studies of substrate and solvent isotope effects and product labeling experiments are not complicated by a significant exchange of boron-bonded hydrogen or deuterium with solvent.

The reaction of morpholine–borane-d_3 with acetone at pH 5 or 3.1 gives exclusively the C-deuterated alcohol, $(CH_3)_2CDOH$. The ^1H nmr spectrum, obtained on a CCl_4 solution of the alcohol isolated from the reaction mixture, shows a singlet at δ −1.16 ppm (assigned to the methyl protons) relative to tetramethylsilane as internal standard.[8] No splitting of this signal was observed, whereas unlabeled 2-propanol in CCl_4 shows a doublet centered at δ −1.13.[9] Also there was no evidence for the multiplet (arising from the splitting of the carbinol hydrogen signal) which in unlabeled 2-propanol is found at δ −3.90 ppm. The hydrogen which becomes attached to the carbonyl carbon atom upon ketone reduction, therefore, originates in the hydride of the amine–borane.

(8) Small amounts of acetone are indicated by a singlet at $\delta = -2.13$.
(9) "N.M.R. Spectra of Common Impurities," The Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1967, p 15.

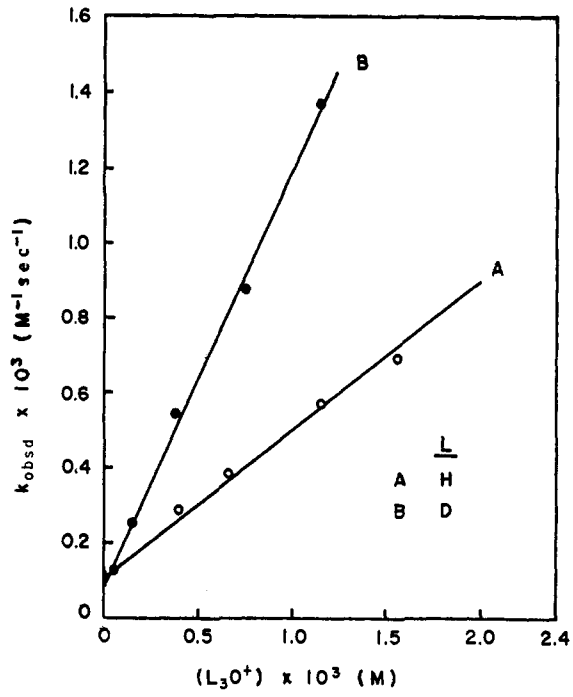

Figure 1. The lyonium ion dependence of the rate of reduction of acetone by morpholine–borane at 25°.

Isotope Effects. The dependence of the rate of reduction of acetone on acidity in water and deuterium oxide is shown in Table II and Figure 1. Rate constants characterizing the acid-independent and acid-catalyzed pathways (k_1 and k_2, respectively) are equal to the *y* intercepts and slopes of the respective lines. Only a small change in rate of the acid-independent path is caused by a shift from water to deuterium oxide, whereas a significant solvent isotope effect [$k_2(D_2O)/k_2(H_2O) = 2.8$] is observed for the acid-catalyzed reaction. Normal substrate isotope effects of about 10 and 20% were obtained for the acid-independent and acid-catalyzed reactions, respectively (Table III). Although these effects were rather insensitive to changes in temperature over the range 10–40°, the volatility of acetone severely limits the extent to which a temperature dependence of the isotope effect can be reliably determined.

Table II. Rates of Reaction of Morpholine–Borane with Acetone in H_2O and D_2O at 25°

Lyonium ion, $M \times 10^3$	$k_{obsd} \times 10^3$, M^{-1} sec^{-1} H_2O	D_2O
0.01	0.096	0.093
0.05		0.13
0.16		0.25
0.38		0.55
0.39	0.29	
0.66	0.38	
0.75		0.87
1.15	0.57	1.4
1.55	0.69	
$k_1 \times 10^3$, M^{-1} sec^{-1}	0.096	0.093
k_2, M^{-2} sec^{-1}	0.40	1.1

Alkyl Substitution, Solvent Effects, and Activation Parameters. Data obtained for acetone, methyl ethyl

Table III. Substrate Isotope Effects for the Reaction of Morpholine–Borane with Aqueous Acetone at Various Temperatures

Temp, °C	$k_{1H} \times 10^3$, M^{-1} sec^{-1}	$k_{1D} \times 10^3$, M^{-1} sec^{-1}	k_{1H}/k_{1D}	k_{2H}, M^{-2} sec^{-1}	k_{2D}, M^{-2} sec^{-1}	k_{2H}/k_{2D}
10	0.032	0.030	1.1	0.17	0.14	1.2
25	0.096	0.087	1.1	0.40	0.33	1.2
30	0.13	0.12	1.1	0.63	0.52	1.2
40	0.23	0.21	1.1	1.0	0.89	1.1

ketone, and methyl *t*-butyl ketone show an increase in k_1 and k_2 with increasing alkyl substitution at the α carbon atom of the carbonyl (Table IV). Correlations between respective log k values and Taft σ^* parameters[10] are shown in Figure 2. Small changes in the dioxane–water content of the solvent show only a minor effect on the rate of the acid-independent reaction. Thus, for solutions of 60, 50, and 40% (by volume) dioxane, respective values of $k_1 \times 10^3$ are (at 25°) 0.029, 0.036, and 0.046 M^{-1} sec^{-1}. A plot of log k_1 *vs.* the appropriate Grunwald–Winstein Y value[11,12] leads to $m = +0.13$. The effect of temperature on rate is shown in Table III and Figure 3. Activation parameters are given in Table V.

Table IV. Correlation of Rates of Reduction of Methyl Alkyl Ketones with Taft σ^* Values[a]

Ketone	$k_1 \times 10^3$, M^{-1} sec^{-1}	k_2, M^{-2} sec^{-1}	σ^*
CH_3COCH_3	0.096	0.40	0.0
$CH_3COCH_2CH_3$	0.16	0.55	−0.10
$CH_3COC(CH_3)_3$	0.65	0.90	−0.30

[a] See ref 10. Temperature = 25°.

neutral aqueous acetone.[3] To summarize briefly, the rate-determining step is presumed to involve attack of amine–borane on the ketone with concurrent or subsequent hydride transfer from boron to carbon. The fate of the two remaining hydridic hydrogen atoms (per BH_3 unit) is attributed to the results of competition between ketone and solvent (water) for reactive hydridic intermediates, presumed to include hydroxyboranes, formed *after* the rate-determining step.

The observed product distribution at pH 3.1 then presumably reflects the results of competition between ketone and solvent for hydride-containing intermediates formed *via both* acid-independent and acid-dependent paths. Since, as is the case in neutral solution, product distribution data at pH 3.1 indicate no less than one-third of the available hydride to be used for reduction of ketone even in dilute solution, and since product labeling shows that hydride is transferred from boron to carbon, it seems reasonable to presume that the rate-limiting step of the acid-dependent path also involves attack of some form of amine–borane on some form of the carbonyl leading to the use of one of the three available hydridic hydrogens for ketone reduction. For given acetone concentrations above 1 M, however, more hydride is lost *via* hydrolysis at pH 3.1 than at pH 5, suggesting that in the more acidic solution, ketone is less successful in competing with water for available hydride containing intermediates. If the same intermediates are formed *via* both pathways then the observed product distribution data may represent a greater sensitivity to acid catalysis of the hydrolysis of such intermediates relative to their reactions with ketone.

Table V. Activation Parameters for the Reduction of Acetone

Substrate	$\Delta H_1^{\ddagger}$, kcal/mol	d[a]	$\Delta S_1^{\ddagger}$,[b] eu	d[a]	$\Delta H_2^{\ddagger}$, kcal/mol	d[a]	$\Delta S_2^{\ddagger}$,[b] eu	d[a]
$O(CH_2)_4NHBH_3$	11.0	0.2	−40	1	10.2	0.6	−26	2
$O(CH_2)_4NHBD_3$	10.7	0.3	−41	1	10.6	0.6	−25	2

[a] d = square root of estimated variance × 1.987. [b] $\Delta S^{\ddagger}$ at 30°.

Other Carbonyl Reductions. For the morpholine–borane reduction of p-$CH_3OC_6H_4CHO$ at 25°, $k_1 = 0.69 \times 10^{-3}$ M^{-1} sec^{-1}, $k_2 = 1.4$ M^{-2} sec^{-1}. For p-$HOC_6H_4COCH_3$, $k_1 = 7.8 \times 10^{-6}$ M^{-1} sec^{-1}, $k_2 = 0.095$ M^{-2} sec^{-1}.

Discussion

It is convenient to consider the system in terms of the classifications discussed by Langford and Gray,[13] whereby a statement of the sequence of elementary steps is considered one of *stoichiometric* mechanism and a statement of details of individual steps, including bond-breaking and bond-forming processes, one of *intimate* mechanism. For the acid-independent reaction, a series of elementary steps was proposed earlier on the basis of observed product distribution in

With respect to the stoichiometric mechanism of the acid-dependent reaction, the direction and magnitude of the observed solvent isotope effect [$k_2(D_2O)/k_2(H_2O) = 2.8$] argue strongly in favor of the protonation of a substrate in a fast preequilibrium step followed by a rate-determining reaction of the protonated species. It seems reasonable that it is the carbonyl compound which becomes protonated, in which case the observed

$$CH_3COCH_3 + H_3O^+ \rightleftharpoons [(CH_3)_2COH]^+ + H_2O \quad \text{(fast)} \quad (2)$$

$$O(CH_2)_4NHBH_3 + [(CH_3)_2COH]^+ \xrightarrow{k_r} \quad \text{(slow)} \quad (3)$$

rate constant, k_2, will be the product of the equilibrium constant for the protonation of ketone (eq 2) and rate

(10) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **74**, 3120 (1952); **75**, 4231 (1953).
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(12) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).
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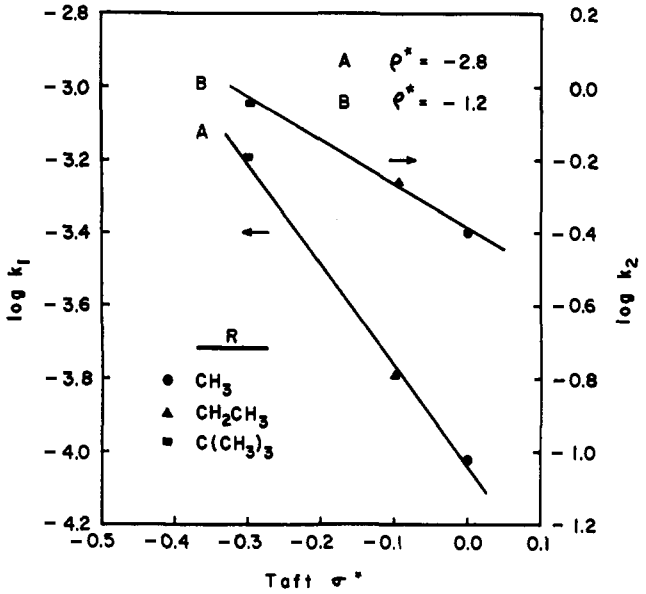

Figure 2. Correlation of the rates of the morpholine–borane reduction of methyl alkyl ketones (CH_3COR) with Taft σ^* values.

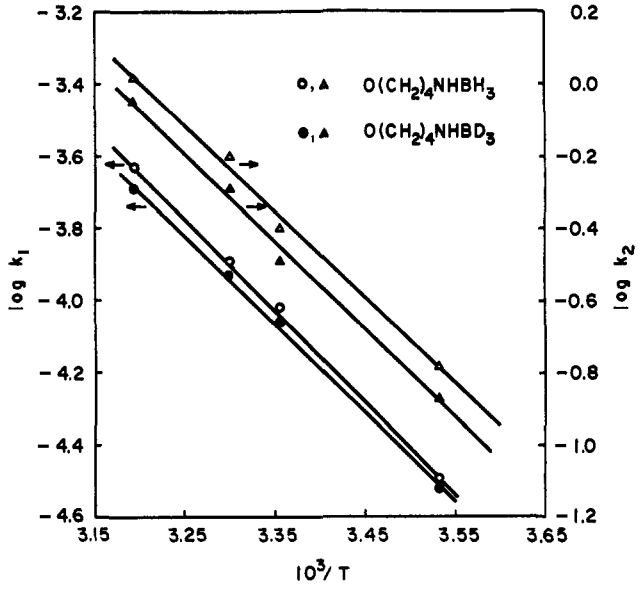

Figure 3. Temperature dependence of the rates of the uncatalyzed and acid-catalyzed reductions of acetone by morpholine–borane and morpholine–borane-d_3.

constant k_r. Numerous examples of solvent isotope effects of comparable magnitude have been reported for reactions thought to be mechanistically similar.[14,15] For example, the first step is the same as that proposed for the acid-catalyzed enolization of acetone, a reaction found to exhibit $k(D_2O)/k(H_2O) = 2.1$ for catalysis by lyonium ion.[14,16] The nature of species formed in the rate-determining step and those subsequent to it is, at this point, a matter of speculation. Possibly isopropoxyborane is formed with hydrolysis of the borate linkage then giving hydroxyborane(s) as proposed for the acid-independent path.[3]

Also speculative are statements of *intimate* mechanism including representation of the corresponding transition states. Considering first the uncatalyzed path, the small solvent effect observed in aqueous dioxane indicates the difference between the degree of solvation of reactants and activated complex to be small. This precludes a large contribution to the entropy term due to changes in solvation and suggests that the major contribution to the large negative entropy of activation (−40 eu) is the formation of a relatively highly ordered activated complex from neutral reactants.

The substrate hydrogen isotope effect is not unambiguous, since although a small isotope effect is predicted for a transition state in which the extent of boron–hydrogen bond cleavage is slight, other explanations have been offered for the small effects reported in numerous reactions presumed to involve hydride transfer from boron.[17–20] For example, the small effect observed in the hydrolysis of substituted pyridine–diarylboranes has been suggested to be compatible with a nonlinear transition state in which only partial loss of the B–H stretching vibration has occurred.[17,18] Experimental k_H/k_D values observed for the hydrolysis of pyridine–monoarylboranes[19] and the *inverse* isotope effect found in the hydrolysis of tetrahydroborate ion[21] have been suggested to be due to significant inverse secondary isotope effects,[22] although Halevi has interpreted such inverse isotope effects to be predominantly primary in origin.[23] Returning to the morpholine–borane reduction of acetone, the small substrate isotope effect is consistent with a transition state in which hydride transfer from boron to carbon has not proceeded very far, but cannot be construed as unequivocal evidence for such a model. Bond formation between carbon and hydridic hydrogen in the transition state would contribute to a reduction in the value of k_H/k_D.

The linear correlation of rate with the Taft σ^* parameter suggests that the enhancement of rate accompanying an increase in alkyl substitution at the α carbon atom is primarily due to the polar inductive effect of the substituent. This may be an acceleration due to the transmission of electron density to a nucleophilic site, perhaps the carbonyl oxygen, suggesting that boron–oxygen bond formation may be important in the activated complex. Although the inductive effect expected for formation of a carbon–hydrogen bond *via* hydride transfer from boron would be in the opposite direction, this does not rule out the possibility of some hydride transfer occurring in the rate-determining step. The pK_a values for the conjugate acids of acetone (−7.2), methyl ethyl ketone (−7.2), methyl isopropyl ketone (−7.1), and methyl *t*-butyl ketone (−7.1) have been obtained from ultraviolet data,[24,25]

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(15) (a) This appears to be an example of catalysis described as case I (case II if the rate-determining step involves proton transfer from the protonated substrate); see A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 9; (b) alternatively designated as an A-2 mechanism: F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 935 (1957).
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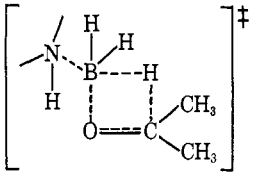
(22) An inverse isotope effect ($k_D/k_H = 1.6$) also has been observed for the reaction of $LiBH_4$ with methanol in diglyme; see R. E. Dessy and E. Grannen, Jr., *ibid.*, **83**, 3953 (1961).
(23) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 214 (1963).

and the value for acetone was confirmed by independent studies of Raman and nmr spectra.[26] While there is no apparent correlation of ketone basicity with rates of reduction by amine–borane, it is interesting that Campbell and Edward[25] have suggested that probably "the tendency for basicity to be increased by the inductive effect of an increasing number of alkyl groups on the α-carbon atom is offset by the effect of these groups in restricting the stabilization of the protonated ketone by solvation." It may be that the trend in the rates of reduction by amine–borane serves as a better indication of the inductive effect of the substituents than do the basicities of the ketones.

It seems reasonable to consider the transition state for the acid-independent path to be one in which the amine–borane and ketone have become quite specifically oriented with respect to one another with consequent loss of some rotational degrees of freedom and where some bond formation is occurring between boron and oxygen. "Four-center" transition states have been proposed for such reactions as the hydroboration of olefins,[27] the solvolysis of BH_4^-,[22] and the hydrolysis of borazine derivatives,[28] and one consideration here is a "four-center" model in which boron and hydrogen are added across the carbonyl group. There is no evidence for or against breaking of the boron–nitrogen bond, although if this bond is not broken in the rate-determining step, it must be shortly thereafter if isopropoxyborane is to be formed as an intermediate. It is suggested that some loosening of the boron–nitrogen bond accompanies coordination of boron to oxygen with some concerted hydride transfer also occurring in the transition state. Collapse of such an activated complex (I) would give isopropoxyborane as a reactive intermediate with subsequent hydrolysis giving isopropyl alcohol, hydrogen, and borate, presumably through formation of hydroxyboranes.[3]



I

Early studies of the reduction of carbonyl compounds (including acetone) with diborane, led Brown and coworkers to propose a mechanism which involved the rate-determining formation of a carbonyl–borane complex followed by a rapid hydride transfer from boron to carbon.[29] Jones also has suggested a similar mechanism for the reduction of 4-*t*-butylcyclohexanone with trimethylamine–borane (and diborane) in neutral nonaqueous solvents.[30] Four-center transition states have been proposed for the intramolecular transfer of hydride in such intermediates.[30,31] A similar mechanism for the morpholine–borane reduction of acetone, viewed as a rate-determining nucleophilic attack of the keto oxygen on boron with displacement of morpholine to give the intermediate complex, $(CH_3)_2\overset{+}{C}O\bar{B}H_3$, followed by a fast hydride transfer, should be considered. If the formation of such a complex were rate determining, the observed isotope effect would be a secondary one. The relatively low activation energy suggests, in terms of Hammond's postulate, that not a great deal of molecular reorganization is required to reach the transition state (the entropy term constitutes a major contribution to $\Delta F^{\pm}$).[32] Also, if a highly unstable keto–borane intermediate complex is obtained, one expects only slight rearrangement, probably with minimal boron–hydrogen bond breaking, for this complex to get to the transition state for its subsequent collapse, *via* intramolecular hydride transfer, to isopropoxyborane. Such a transition state will probably look very much like the complex itself. Thus, a "concerted" mechanism for the amine–borane reduction of ketone, in which hydride is transferred in the rate-determining step, even where the transition state may be reached with only a small degree of weakening of the boron–hydrogen bond, seems as consistent as one involving the rate-determining formation of a highly unstable keto–borane complex. Thus, there is no compelling evidence that a keto–borane intermediate is kinetically significant. Further, there may be some difficulty in rationalizing formation of a keto–borane complex with the observed activation enthalpy of 11 kcal. Although data are not available to permit calculation of the enthalpy requirement for displacement of amine from morpholine–borane by acetone, it is possible to estimate ΔH for comparable displacements by stronger Lewis bases. Thus, from reported values of the enthalpy of the vapor-phase dissociation of trimethylamine–borane (31.5 kcal/mol)[33] and dimethyl sulfide–borane (20 kcal/mol),[34] an enthalpy of 11–12 kcal/mol is estimated for the reaction $(CH_3)_3NBH_3$ (g) + $(CH_3)_2S$(g) → $(CH_3)_2SBH_3$(g) + $(CH_3)_3N$(g). Quantitative data on the difference in basicity of acetone and dimethyl sulfide toward $-BH_3$ are not available (ΔpK_a values may be quite misleading since they reflect differences in tendencies to coordinate hydrogen ion which for some bases, *e.g.*, dimethyl sulfide and dimethyl ether, are inverted relative to their basicities toward $-BH_3$). Nevertheless, from a comparison of data on the dissociation of various addition compounds, it seems clear that dimethyl sulfide–borane will exhibit a significantly lower vapor-phase dissociation constant than will acetone–borane. If such equilibria can be taken as a measure of relative enthalpies of dissociation,[35] then it seems reasonable that the vapor-phase displacement of amine from $(CH_3)_3NBH_3$ by acetone will require an enthalpy considerably in excess of 12 kcal. Although the present argument involves numerous assumptions of analogy between the solution reaction under study and vapor-phase dissociation of different donor–borane adducts, it seems

(24) J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Can. J. Chem.*, **38**, 1518 (1960).
(25) H. J. Campbell and J. T. Edward, *ibid.*, **38**, 2109 (1960).
(26) N. C. Deno and M. J. Wisotsky, *J. Amer. Chem. Soc.*, **85**, 1735 (1963).
(27) H. C. Brown and G. Zweifel, *ibid.*, **82**, 4708 (1960).
(28) T. Yoshizaki, H. Watanabe, and T. Nakagawa, *Inorg. Chem.*, **7**, 422 (1968).
(29) H. C. Brown, H. I. Schlesinger, and A. B. Burg, *J. Amer. Chem. Soc.*, **61**, 673 (1939).
(30) W. M. Jones, *ibid.*, **82**, 2528 (1960).
(31) A. B. Burg, *J. Chem. Educ.*, **37**, 482 (1960).
(32) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(33) R. E. McCoy and S. H. Bauer, *ibid.*, **78**, 2061 (1956).
(34) T. D. Coyle, H. D. Kaesz, and F. G. A. Stone, *ibid.*, **81**, 2989 (1959).
(35) It has been shown through studies in the vapor phase that "for many closely related adducts of group III elements, entropy changes accompanying dissociation are rather similar;" see F. G. A. Stone, *Chem. Rev.*, **58**, 101 (1958).

not unlikely that the enthalpy of formation of a keto–borane complex from morpholine–borane and acetone may well lie in excess of 11 kcal/mol. Since the activation enthalpy would have to be at least equal to the endothermicity of formation of this complex, the observed value of $\Delta H_1^{\ddagger}$ argues against such a complex as a reactive intermediate.[36]

It is interesting that the model suggested for the intimate mechanism of the reaction of morpholine–borane with neutral acetone is somewhat analogous to those proposed for numerous diene syntheses and cycloaddition reactions in solution, *e.g.*, cyclopentadiene dimerization, which presumably proceed by bimolecular association. The analogy is supported by the fact that the reactions have similar activation parameters (low enthalpies and highly negative entropies of activation) and also exhibit rates which are relatively independent of changes in solvent character.[37–39] Presumably, both reactions involve highly "ordered" activated complexes.

An interpretation of effects influencing the rate of the acid-dependent reaction is complicated by the fact that k_2 is presumed to be the product of two terms, the equilibrium constant for protonation of the ketone and the rate constant for the subsequent rate-determining step. Assuming the pK_a for protonated acetone to be -7.2, one obtains a value at 30° of $k_r \sim 10^7\ M^{-1}\ sec^{-1}$, suggesting the enormous effect ($k_r/k_1 \sim 10^{11}$) of protonation on the susceptibility of the carbonyl compound to attack by amine–borane. The reported acidities of the corresponding protonated ketones, however, do not enable a reliable conclusion to be drawn as to the effect of C-alkyl substitution on k_r. That is, the measured substituent effects are smaller than the uncertainty in pK_a values (maximum precision of about ± 0.2 pK unit),[25] so that, although it is known that increasing C-alkyl substitution increases k_2, the extent to which this may reflect an influence on K_{eq} as opposed to k_r is not clear. Similarly, although $\Delta H_2^{\ddagger}$ and $\Delta S_2^{\ddagger}$ values are obtained from a plot of log k_2 *vs.* $1/T$, these terms contain, in addition to the activation parameters for the presumed rate-determining step, the standard enthalpy and entropy for protonation of the carbonyl, and data for the temperature dependence of the acidity constant needed to evaluate such terms are not available. Thus, observed substituent effects and activation parameters, although helpful in characterizing the system, do not offer particular insight into the intimate mechanism of the rate-determining step. Nor is the small substrate isotope effect (~20%) particularly definitive. A rather unsatisfactory representation of this transition state will probably remain at least until appropriate data become available to permit the separation of individual effects on K_{eq} and k_r.

It has occurred to us, however, that the enhancement of rate caused by protonation of the carbonyl may be analogous to the acid catalysis observed in hydrolysis of amine–boranes, which has been proposed to involve a rate-determining electrophilic displacement of BH_3 from nitrogen *via* attack of the proton of a general acid on the adduct. It may be that the protonated carbonyl compounds studied, all of which have extremely high acidities in aqueous solution, serve as very effective general acids for decomposition of the amine–borane linkage. A *cis* displacement of BH_3 is consistent with recently proposed transition state models for acid-catalyzed amine–borane hydrolysis.[40] Although this is quite speculative, it is interesting to compare k_r values calculated from studies of the acid-catalyzed morpholine–borane reduction of acetone (6.4×10^6), *p*-methoxybenzaldehyde (4.9×10^5), and *p*-hydroxyacetophenone ($5.1 \times 10^3\ M^{-1}\ sec^{-1}$) with pK_a values reported for the conjugate acids of these substrates[41] (-7.2,[25,26] -5.5,[42] and -4.7,[43] respectively). Although structural changes in this series are considerable, and while a convincing Brönsted relation is not obtained (nor necessarily expected), the observed increase in k_r with increasing acidity of these conjugate acids may be suggestive of general acid catalysis for their reduction by amine–borane.

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(36) We are indebted to a referee for suggesting that bond making between hydride and carbon may contribute to the reduction of the isotope effect similar to propositions advanced for the alkaline cleavage of organosilanes [see L. Kaplan and K. E. Wilzbach, *J. Amer. Chem. Soc.*, 77, 1297 (1955)], and for suggesting that the low activation enthalpy argues against displacement of amine by unperturbed carbonyl oxygen.

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